DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 23, 2011 has been entered.

Claim 1 has been amended. Claims 1-3 and 7 are under examination in this Office action.

Claim Rejections - 35 USC § 103

Rejection of Claims 1-3 and under 35 U.S.C. 103(a) as being unpatentable over Hillegas et al.(US Patent 6,214,618 B1) in view of Ferrari et al. (US Patent 6,184,348 B1) and Aerts et al. (WO 2004/078955 A1) **is withdrawn** in view of Applicant's amendment.

New Rejection in view of Applicant's amendment

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillegas et al.(US Patent 6,214,618 B1) in view of Ferrari et al. (US Patent 6,184,348 B1), Aerts et al. (WO 2004/078955 A1) and Cherksey (US Patent 5,618,531).

Hillegas teaches methods of producing herpes virus comprising adhering cells to a microcarrier support comprising multiple copies of the cell attachment ligand the fibronectin cell binding domain, Arg Gly Asp (RGD) peptide of present SEQ ID NO: 70 (see claims 1-13, column 2, lines 19-41, column 3, lines 15-27, column 4, lines 35-62, and Example 2). The method taught by Hillegas further comprises culturing the adhesive cells in a medium free of animal origin components, subculturing the cells using the cell dispersing agent such as EDTA and trypsin and inoculating and proliferating the virus in the cells (see Figures 1-3 and Examples 1 and 2).

While Hillegas teaches Arg Gly Asp (RGD) peptide of present SEQ ID NO: 70 Hillegas does not teach the sequence of Gly Ala Gly Ala Gly Ser (GAGAGS) of present SEQ ID NO: 74. Hillegas does not teach the number-average molecular weight (Mn). Hillegas teaches EDTA and trypsin but he does not teach protease originated from a plant.

Ferrari teaches polymer polypeptides Gly Ala Gly Ala Gly Ser (GAGAGS) of present SEQ ID NO: 74 and Arg Gly Asp (RGD) peptide of present SEQ ID NO: 70 bonded together in a tandem repeat (see claims 4 and 5, and SEQ ID NO: 119 identical with present SEQ ID NO: 74). Ferrari teaches that the polymer peptide contains repeating units of Gly Ala Gly Ala Gly Ser (GAGAGS) of present SEQ ID NO: 74 and Arg Gly Asp (RGD) (see claims 1-14). Ferrari teaches molecular weight of the GAGAGS and RGD polymers from 90, 150, 250, 300, 500 to 3640 kDal (see Example 3). Ferrari teaches that the GAGAGS and RGD polypeptides are cell growth and attachment factors promoting the growth of cells in a tissue culture (Example 3).

Regarding the new limitation of the support consisting of nylon, Ferrari teaches nylon fibers used for purification of various molecules (see columns 47 and 48, lines 10-25). However

Ferrari does not provide a motivation to use the nylon support for growing cells producing a virus.

Ferrari does not teach protease originated from a plant or a genetically recombinant bacteria.

Aerts teaches methods of producing a virus (*Herpesviridae, Orthomyxovirus, Poxviridae* and other) in animal-free cell culture comprising seeding the cells in cell culture medium free of animal components and letting the cells to adhere to the substrate, detaching the cells from the substrate using cell dispersing agent free from animal components such as protease originated from a plant or genetically recombinant bacteria, specifically the rProtease (Invitrogen) inoculating and proliferating the virus and growing the cells in the culture medium (see page 12, lines 26-36, page 13, lines 1-5 and 20-37, page 16, lines 10-25, page 18, lines 1-29, pages 26-27, Example 10 and claims 15-36).

Cherksey teaches methods for increasing the viability of cells comprising growing cells on nylon bead matrices (see claims 1-16 and column 5, lines 26-44). Cherksey teaches adhering and growing cells on matrices comprising nylon beads (see column 11, lines 53-67).

It would have *been prima* facie obvious and one would have been motivated to provide Hillegas method of producing a virus using the microcarrier support comprising Ferrari's polymer polypeptides Gly Ala Gly Ala Gly Ser (GAGAGS) and Arg Gly Asp (RGD) because Ferrari teaches that the GAGAGS and RGD polypeptides are cell growth and attachment factors promoting the growth of cells in a tissue culture (Example 3). Absent unexpected results, it would have been prima facie obvious to provide 5 sequences of RGD peptide and 5 sequences of 3 times the GAGAGS peptide.

It would have *been prima* facie obvious to provide Hillegas method of producing a virus comprising subculturing the adhesive cells in Aerts' protease free of animal origin, originated from a plant or genetically recombinant bacteria because Aerts teaches to substitute the protease free of animal origin for animal derived trypsin. Aerts teaches the use of animal free cell culture components such as animal free medium and animal free protease instead of using animal derived medium or animal derived trypsin, in order to avoid the disadvantages of animal component in a cell culture such as: batch to batch variability, the association with higher contamination risk by adventitious agents, and difficulties encountered in downstream processing such as purification (see page 2, lines 16-25).

Regarding the limitation of nylon support, it would have *been prima* facie obvious to provide Hillegas method of producing a virus comprising subculturing the adhesive cells in Cherksey's nylon bead matrices because Cherksey teaches that growing adhesive cells in nylon bead matrices increases the viability of the cells. It would have been obvious that increased viability of the cells would support the virus replication in the cells.

It would have been obvious to optimize the amount and the molecular weight of the polymer polypeptides Gly Ala Gly Ala Gly Ser (GAGAGS) and Arg Gly Asp (RGD) to arrive at about 20,000 Mn. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). Optimizing experimental conditions, including the amount of the compound used, falls within the skills of an ordinary artisan. If the amount of the polymer used in the claimed methods produces an unexpected result, applicant needs to point out what the unexpected results are.

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Thus the present invention would have been prima facie obvious to the skilled artisan at the time when the invention was made.

Response to Applicant's argument

In response to Applicant's argument that neither Hillegas, Ferrari nor Aerts teach the newly amended limitation of support consisting essentially of nylon, the Examiner notes that the reference by Cherksey teaches methods for increasing the viability of cells comprising growing cells on nylon bead matrices, as discussed in the above rejection.

Applicant argues that the present specification shows that support consisting essentially of nylon has unexpected benefits relative to other supports in terms of cell density.

In response, it is noted that contrary to Applicant's assertion, paragraphs 126-140 in the specification do not show that using nylon support has unexpected benefits relative to other supports in terms of cell density. It is noted that the nylon beads used in Example 1 are coated with ProNection while the dextran beads in comparative examples 1, 2 and 3 are coated with pig collagen, or not coated at all. Table 1 on page 20 shows that sample 4 where the ProNection nylon beads were used had the same cell density as sample 2 (using dextran beads), however more virus was produced in sample 4 (using ProNection coated nylon beads). Applicant's argument regarding the unexpected benefits relative to other supports in terms of cell density is

not found persuasive because Applicant's specification shows that cell density is the same either nylon or dextran beads are used (see Table 1 cell number for samples 2 and 4). The virus titer is the highest when ProNection nylon beads are used, however that may be due to the action of ProNection and not necessarily due to the type of the support used. Applicant's examples do not compare two types of beads both coated with ProNection. Because there are other factors such as ProNection (besides the type of the support) that are present in Applicant's working examples, the skilled artisan would have been unable to conclude that the nylon support contributes to the unexpected results argued by Applicant. Thus Applicant's argument about the unexpected results is not found persuasive. Additionally, the skilled artisan would have expected increased virus production from cells grown on the nylon beads because Cherksey teaches that the nylon bead support increased the viability of the adhesive cells, as discussed in the rejection above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AGNIESZKA BOESEN whose telephone number is (571)272-8035. The examiner can normally be reached on 9:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Agnieszka Boesen/

Primary Examiner, Art Unit 1648